RESEARCH ARTICLE

Individualized Chemotherapy for Metastatic Gastric Cancer: Retrospective Data from a University Hospital in Brazil

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Abstract

Background: Despite the decreased incidence, gastric cancer is still a frequent cause of cancer related death. The 1st line 2 or 3 drugs regimen is still a debatable issue. HER2 targeted therapy has emerged as the standard of care, but it is unavailable in the Brazilian Public Health System. The end-point of this trial was overall survival (OS) in patients with metastatic gastric cancer treated in a public university hospital in Brazil. The secondary end-points were efficacy and safety of regimens with 2 (F+P) or 3 (EOX) drugs to develop an institutional guideline to facilitate optimal treatments. Materials and Methods: In this retrospective study, 1st line regimens were evaluated for OS and PFS stratified by age and ECOG using Cox regression. Results: 47 patients were treated over the last 3 years. In 1st line, 29 were treated with F+P (mean 59.3 years, 34.5% ECOG 2 and a mean of 5.69 cycles) and 16 with EOX (mean 47 years, 18.8% ECOG 2 and a mean of 5.44 cycles). The median OS was 13.8 months (95%CI 10.7-16.9). Response was evaluated in 40 cases and was 64.3% for EOX and 37.5% for F+P (p=0.25). The median PFS was 9.5 months for EOX and 5.6 months for F+P (HR 0.85, 95%CI 0.41-1.74). However, among patients with ECOG 2 mPFS was 3.70 vs 5.40 months, respectively (p=0.86). Regimens showed similar manageable adverse events. A total of 34 patients suffered progression and 14 received 2nd line therapy. Diffuse histology (HR 1.89, 95%CI 1.22-2.88), achieving 2nd line (HR: 0.25, 95%CI 0.11-0.58) and treatment response (HR 0.23, 95%CI 0.12-0.47) were OS prognostic factors. Conclusions: Patients treated in our hospital had outcomes compatible with the literature. The regimen choice should be related to patient features. Second line treatment should be considered.

Keywords: Gastric cancer - chemotherapy - metastatic - treatment

Asian Pac J Cancer Prev, **16 (13)**, 5289-5296

Introduction

Gastric cancer (GC) is the fifth leading cause of cancer, excluding non-melanoma cancers of the skin, according to the estimates of the National Cancer Institute (INCA) for Brazil in 2014 (INCA, 2014). According to data from the World Health Organization in 2012, GC was the third leading cause of cancer-related deaths worldwide, with a mortality rate that exceeds 70% (Cancer and Organization, 2012). The high mortality associated with GC is mainly observed in patients with advanced stages of the disease. Despite the development of new treatments and better methods of diagnosis, the 5-year survival for patients with stage IV GC is only approximately 4%, whereas patients with stage IA disease show 71% survival at 5 years (Society, 2014; Basaran et al., 2015; Somi et al., 2015). Considering its epidemiological relevance, it is important to conduct an institutional analysis of the treatment of patients with stage IV GC.

Over 90% of GCs are adenocarcinomas. The intestinal Lauren subtype, which has better prognosis, is characterized by a cell arrangement that is similar to that in colorectal adenocarcinomas. The diffuse subtype, which affects mostly young male individuals, is associated with protein E-cadherin mutation, family history, undifferentiated lesions, and an unfavorable prognosis (Cutait et al., 2001).

Regarding the treatment of this disease, a 73% benefit in overall survival (OS) was observed for patients who received chemotherapy compared to those who received best supportive care (hazard ratio [HR] 0.27, 95% confidence interval [CI]: 0.24-0.55, 184 participants) in a meta-analysis that included studies of patients with metastatic GC. The meta-analysis also reported an 18% benefit in OS with multidrug therapy over monotherapy (HR 0.82, 95%CI: 0.74-0.90, 1,914 participants); however, this survival advantage comprised only 1.5 months (Wagner et al., 2010). Moreover, an optimal treatment protocol is yet to be established for these patients.

GC treatment usually involves a combination of fluoropyrimidines and platinum agents. The aforementioned meta-analysis also evaluated the addition of a third drug to the treatment regimen. The addition of anthracyclines as the third drug showed a benefit of 23% in OS (HR 0.77, 95%CI: 0.62-0.95, 501 participants), whereas a combination with docetaxel failed to show a

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statistically significant benefit (HR 0.93, 95%CI: 0.75 - 1.15, 805 participants) (Wagner et al., 2010).

At present, as no specific protocol has proved superior to the others, it is believed that the best chemotherapy regimens should be individualized, based on the patient's clinical characteristics and the oncologist's experience (Bilici, 2014).

Our objective was to evaluate the treatment outcomes of metastatic GC in a university hospital, in order to develop an institutional protocol that can facilitate medical decision-making and promote individualized treatment.

Materials and Methods

Patients

The study population consisted of patients (aged ≥18 years) with a confirmed histological diagnosis of gastric adenocarcinoma and radiologic evidence of metastatic disease. The patients were treated in the Department of Oncology at the Federal University of São Paulo (UNIFESP) between 01/01/2011 and 12/31/2014. Patients who had not received prior systemic treatment, who received at least one complete cycle of chemotherapy, and consented to the use of their personal information by signing the informed consent form, were included.

Study design

This retrospective study followed a quantitative approach. Patient records were accessed and evaluated for epidemiological and clinical data, and for data pertaining to the treatment of metastatic GC. The study was approved by the institutional ethics committee and was conducted in accordance with the provisions of resolution number 466/12, of the Brazilian Ministry of Health.

Treatment protocols

The treatment protocol was chosen by the attending physician, according to clinical and patient intrinsic factors. There was no established institutional protocol to assist the physician with decision making.

The EOX protocol consisted of an intravenous bolus of 50 mg/m^2 epirubicin and 130 mg/m^2 oxaliplatin every 3 weeks, combined with 625 mg/m^2 capecitabine twice daily, administered continuously.

In this study, the protocol described as F+P grouped different chemotherapy protocols, based on combinations of platinum agents and fluoropyrimidines. The preferred and predominant regimen, XELOX, consisted of 130 mg/m^2 oxaliplatin on the first day of the cycle, followed by 1000 mg/m^2 capecitabine twice daily for 14 days, every 3 weeks. In the event that capecitabine was not available, the regimen was modified to Nordic-FLOX that consisted of 85 mg/m^2 oxaliplatin on the first day, followed by a bolus of 500 mg/m^2 5-fluorouracil (5-FU) and 60 mg/m^2 folinic acid for the first 2 days of the cycle, every 2 weeks. The other regimen included in this grouping was CF, which consisted of an intravenous bolus of 70 mg/m^2 cisplatin and 5-fluouracil 1,000 mg/m^2 on for the first five days of the cycle, every 4 weeks.

Other chemotherapy regimens consisted of a 2-hour intravenous infusion of 500 mg/m^2 folinic acid and a bolus infusion of 500 mg/m^2 5-FU, delivered once a week for 6 weeks, with 2 weeks with no chemotherapy. The other single-agent protocol consisted of 1,000 mg/m^2 oral capecitabine administered twice a day for 14 days, every 3 weeks. Monotherapy was administered to <5% of patients, and because of the small sample size, could not be evaluated in terms of efficacy and safety.

Efficacy and safety

The primary endpoint of the study was OS, defined as the time (in months) between diagnosis of the disease and death from any cause. The median OS and 95%CI were compared with values from similar protocols, as reported in the international literature. Secondary endpoints were response rate (RR), median progression-free survival (PFS), and toxicity.

The RR was determined based on the investigator's assessment. The evaluation of imaging examinations was conducted by the radiology team of Hospital Sao Paulo/University Hospital of UNIFESP according to the response evaluation criteria in solid tumors (RECIST) version 1.1 (Therasse et al., 2000). Radiologists were not blinded to patient details. The computed tomography scans were evaluated by different radiologists, under the guidance of the same crew chief. All radiologists were trained to strictly follow the RECIST version 1.1 guidelines. The frequency of imaging studies was usually every 2 or 3 months, according to the recommendation of the respective protocol. The imaging studies have not been re-evaluated by an external team. PFS was defined as the time interval (in months) between the first day of treatment and the first documentation of progression by RECIST, or death from any cause, whichever occurred first (Green and Crowley, 1997). Toxicities were graded in accordance with the common terminology criteria for adverse events (CTCAE) version 4 of the National Cancer Institute (NCI) (Institute, 2009) and were evaluated at regular intervals, and involved documentation of symptoms and adverse changes in the results of laboratory tests performed in the central laboratory of UNIFESP. The patients were evaluated by the same medical staff, and all oncologists were trained and instructed to report adverse events (AEs) according to CTCAE version 4.

The performance status of the patients (from 0 to 5) was determined according to the criteria proposed by the Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982).

Statistical analysis

The epidemiological characteristics of the patient population were evaluated with descriptive statistics for frequencies, measures of central tendency, and proportions.

The OS and PFS analyses were performed using the Kaplan-Meier method. We evaluated the influence of clinical and therapeutic characteristics, which included age, ECOG performance status, histology, number of metastatic sites, response to treatment, and lines of treatment as potential OS prognostic factors, using the stratified log-rank test (Mantel, 1966) and univariate Cox regression analysis (Cox and Oakes, 1990) for each

subgroup. The first-line treatment protocol was evaluated as a prognostic factor for OS and PFS, stratified by age and ECOG performance status. No multivariate tests were performed because of the small sample size and lack of information in medical records for some variables such as histology and response to treatment.

Age was converted into a categorical variable, with a cutoff of 65 years, which is used in most studies and is the United Nations recommended cutoff for elderly individuals. The relationship between the treatment regimen, and the patient's age and ECOG performance status was tested using Pearson's chi-square test. The means for day of chemotherapy initiation were compared for the different ages and ECOG performance status categories using the Student's t- test.

The proportion of patients who had an objective response or toxicity with each first-line treatment protocol was also compared using Pearson's chi-square test.

A statistically significant relationship was considered when p was <0.05, calculated up to two decimal places.

Results

Patients

Forty-seven patients were included in the study. At the time of evaluation, 15 patients remained on treatment and 1 participant relocated to another city after 7 months of follow-up.

Table 1 summarizes the demographic and clinical characteristics of patients included in the study, according to the first- line chemotherapy protocol adopted.

Treatment

On average, chemotherapy began 96 days after diagnosis, this number ranged from 0 to 216 days. The mean number of days for chemotherapy initiation was 63.3 for patients with an ECOG performance status 0, 82.7 for those with an ECOG performance status 1, and 129.6 for those with an ECOG performance status 2 (p=0.03). The mean number of days for chemotherapy initiation was 89.6 for patients <65 years of age, and 112.7 for patients aged ≥65 years (p=0.24). At the end of the study, an average of 6.17 cycles of first-line chemotherapy had been administered.

For the 47 patients included in the study, the main protocols used were F+P and EOX (29 and 16 patients, respectively). The remaining 2 patients received 5-FU or capecitabine monotherapy. Of the 13 patients aged ≥65 years, 2 were treated with monotherapy, 10 with F+P, and 1 with EOX. Of the 34 patients aged <65 years, 19 were treated with F+P, and 15 with EOX (p=0.01). There were 4 patients with an ECOG performance status 0; of these, 3 were treated with F+P and 1 with EOX. Of the 28 patients with an ECOG performance status 1, 16 were treated with F+P and 12 with EOX. Of the 15 patients with an ECOG performance status 2, 2 were treated with monotherapy, 10 with F+P, and 3 with EOX (p=0.19). Of the 16 patients treated with EOX, 6 (37.5%) had 2 or more sites of metastasis; in the F+P arm this proportion was smaller (8/29, 27.6%). This may indicate that EOX is the most favored chemotherapy protocol in young patients in better general clinical condition and with a high burden of disease.

The mean number of chemotherapy cycles was 5.44 for EOX, 5.69 for F+P, and 4.50 for monotherapy. The total number of chemotherapy cycles during the study period was 87 for EOX, 165 for F+P, and 9 for monotherapy. At the time of analysis, 5 patients (17.2%) were undergoing

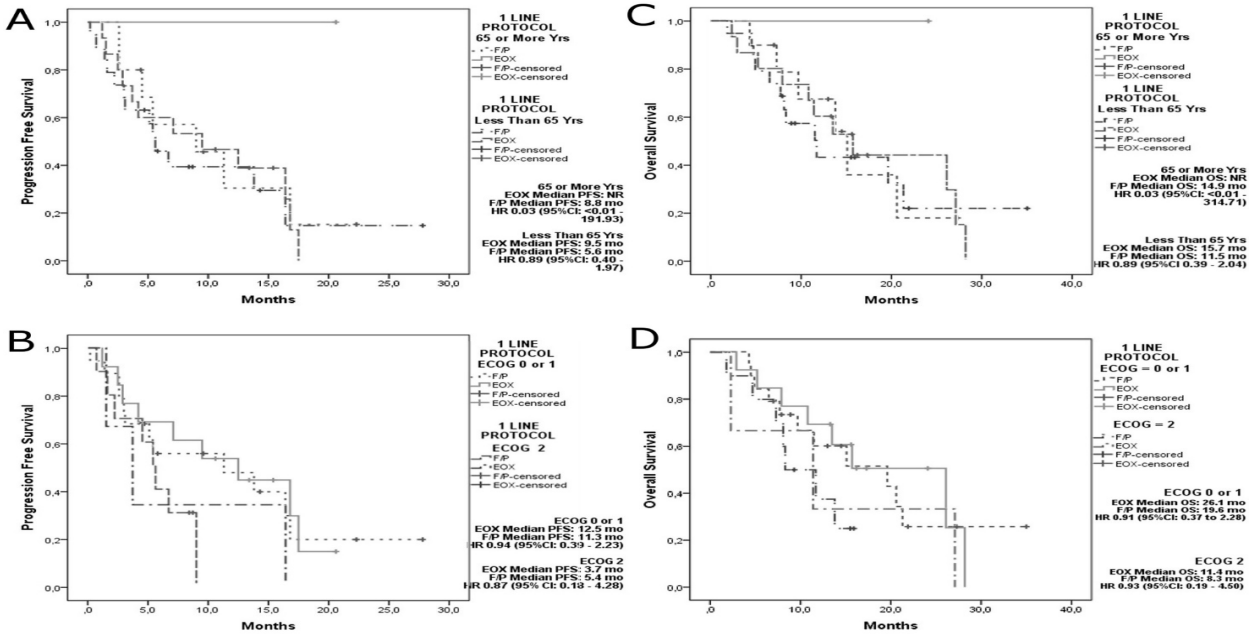

Figure 1. Progression-Free Survival and Overall Survival for different treatment protocols stratified by age and ECOG. A) PFS for different treatment protocols stratified by age; **B)** PFS for different treatment protocols stratified by ECOG; **C)** OS for different treatment protocols stratified by age; **D)** OS for different treatment protocols stratified by ECOG; 1 LINE: First line; Yrs: years; F/P: doublet of fluoropyrimidine and platin; EOX: Epirubicin, Oxaliplatin and Capecitabine; PFS: Progression-Free Survival; NR: not reached; HR: hazard ratio; 95%CI: 95% Confidence Interval; ECOG: Eastern Cooperative Oncology Group; OS: Overall Survival

Table 1. Characteristics of the Patients Studied

		EOX (N = 16)		F + P (N = 29)		F (N = 2)	
Age		Mean	Range	Mean	Range	Mean	Range
		47	27 - 71	59.3	24 - 88	70.5	69 - 72
		N	%	N	%	N	%
Gender	Male	10	62.5%	21	72.4%	2	100%
Region	North/Northeast	9	56.3%	8	27.6%	0	0%
	South/Southeast	7	43.8%	20	69%	2	100%
	NA	0	0%	1	3.44%	0	0%
Ethnic Group	Caucasian	13	81.3%	21	72.4%	1	50%
	Afrodescendant	3	18.8%	6	20.7%	1	50%
	Asiatic	0	0%	1	3.45%	0	0%
	NA	0	0%	1	3.45%	0	0%
ECOG	0	1	6.25%	3	10.3%	0	0%
	1	12	75%	16	55.2%	0	0%
	2	3	18.8%	10	34.5%	2	100%
Smoking		9	56.3%	18	62.1%	1	50%
Alcoholism		5	31.3%	12	41.4%	1	50%
Weight Loss higher > 10 % in 6 months		10	62.5%	23	79.3%	2	100%
Comorbidities		5	31.3%	11	37.9%	2	100%
Congestive Heart Failure		0	0%	4	13.8%	1	50%
2 or more metastatic sites		6	37.5%	8	27.6%	0	0%
Histology	Well Differentiated	2	12.5%	2	6.9%	0	0%
	Mod Differentiated	3	18.8%	9	31%	2	100%
	Poor Differentiated	1	6.3%	3	10.3%	0	0%
	NA	4	25%	5	17.3%	0	0%
Tumor Location	Antrum-Pylorus	3	18.8%	10	34.5%	0	0%
	Body	10	62.5%	13	44.8%	1	50%
	EGJ	3	18.8%	3	10.3%	1	50%
	Fundus-Cardia	0	0%	3	10.3%	0	0%
CEA	Elevated	8	50%	10	34.5%	0	0%
	NA	2	12.5%	10	34.5%	1	50%
Anemia	Yes	5	31.3%	17	58.6%	2	100%
	NA	0	0%	3	10.3%	0	0%
Days to Start Chemotherapy		Mean	Range	Mean	Range	Mean	Range
		92.1	0-203	91.5	8-216	193	192-194

Legends: EOX: Epirubicin, Oxaliplatin and Capecitabine; F+P: Fluoropyrimidine and Platinum; F: Fluoropyrimidine Monodrug; NA: Not Available; ECOG: Performance was evaluated according to guidelines of the Eastern Cooperative Oncology Group; with a score of 0 indicating normal performance status, 1 mildly symptomatic, 2 symptomatic but in bed less than half the day, 3 symptomatic and in bed more than half the day, and 4 in bed the whole day.; EGJ: esophagogastric junction; CEA: Carcinoembryonic Antigen

treatment with F+P. The main reasons for discontinuation of first-line treatment were progression of disease (11 [37.9%] and 5 [31.3%] patients treated with F+P and EOX, respectively), a decrease in performance status (6 [20.7%] and 4 [25%] patients treated with F+P and EOX, respectively), AEs (4 [13.8%] and 3 [18.8%] patients treated with F+P and EOX, respectively), and achievement of maximum response (2 [6.90%] and 3 [18.8%] patients treated with F+P and EOX, respectively).

Efficacy

Objective Response Rate: At the time of analysis, 40 patients were evaluated for treatment response (14 of 16 patients treated with EOX, 24 of 29 with F+P, and 2 of 2 treated with monotherapy). Patients treated with the EOX regimen had higher objective response rate than patients treated with F+P (64.3% and 37.5%, respectively); however, this difference was not statistically significant (p=0.25) (Table 2).

Progression-free and Overall Survival: The median PFS was 7.1 months (95%CI: 2.2 - 12.0). The median OS was 13.8 months (95%CI: 10.7 - 16.9). No statistically significant difference was observed between patients treated with EOX or F+P for PFS (HR: 0.85, 95%CI:

0.41-1.74, p=0.64), and OS (HR: 0.85, 95%CI: 0.40-1.82, p=0.68).

For patients aged ≥65 years treated with F+P, the median PFS was 8.8 months and the median OS was 14.9 months; only 1 participant was treated with EOX and is still alive, without disease progression after 20 months of follow-up. For patients aged <65 years, EOX showed no statistically significant difference in PFS (median 9.5 versus 5.6 months, HR 0.89, 95%CI: 0.40-1.97) and OS (median 15.7 versus 11.5 months, HR 0.89, 95%CI: 0.39-2.04) compared to F+P. For patients with an ECOG performance status 0 or 1, compared to F+P, EOX resulted in superior PFS (median 12.5 versus 11.3 months, HR 0.94, 95%CI: 0.39-2.23) and OS (median 26.1 versus 19.6 months, HR 0.91, 95%CI: 0.37-2.28); however, these results were also not statistically significant. For patients with an ECOG performance status 2, the differences were still not statistically significant, however, compared to F+P, EOX showed a worse PFS (median 3.7 versus 5.4 months, HR 0.87, 95%CI: 0.18-4.28). Figure 1 summarizes the PFS and OS for the first-line chemotherapy protocols, stratified by ECOG performance status and age.

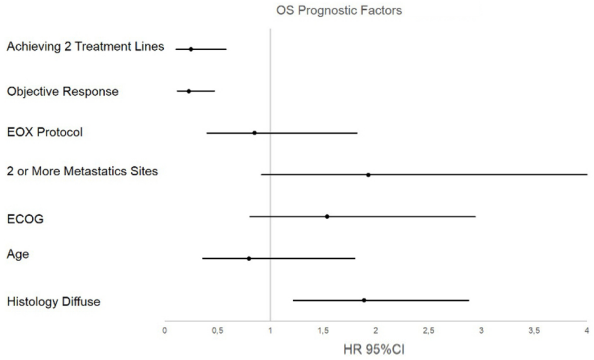

Figure 2. Prognostic Factors for Overall Survival. OS: Overall Survival; HR: Hazard Ratio; 95%CI: 95% Confidence Interval; EOX: Epirubicin, Oxaliplatin and Capecitabine; ECOG: Eastern Cooperative Oncology Group

Table 2. Response to the Treatment

	EOX (N=16)	F + P (N=29)	F (N=2)
Evaluated	14 (100%)	24 (100%)	2 (100%)
Objective Response	9 (64.3)	9 (37.5)	1 (50)
Complete Response	1 (7.14)	0 (0)	0 (0)
Partial Response	8 (57.1)	9 (37.5)	1 (50)
Stable Disease	2 (14.3)	8 (33.3)	0 (0)
Progressive Disease	3 (21.4)	7 (29.2)	1 (50)

Legend: EOX: Epirrubicin, Oxaliplatin and Capecitabine; F+P: Fluoropyrimidine and Platinum; F: Fluoropyrimidine

Subgroup Analysis

Subgroup analysis was performed according to the clinical and therapeutic characteristics of patients, considering their potential influence on survival (Figure

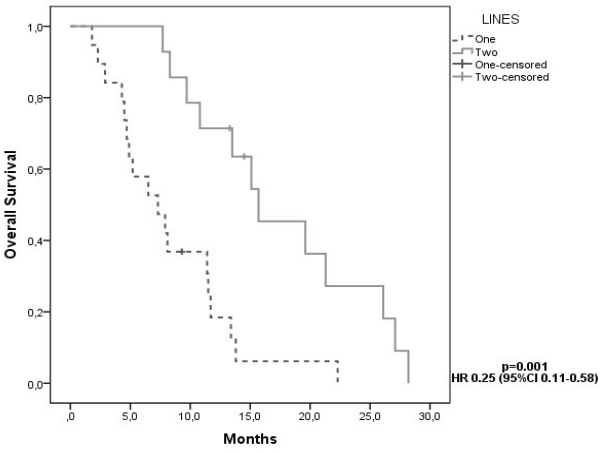

Figure 3. Kaplan-Meier Survival Analysis for Patients whom Received one or Two Lines of Treatment. HR: Hazard Ratio; 95%CI: 95% Confidence Interval

Table 3. Main Adverse Events

	EOX (N = 16)		F + P (N = 29)		F (N = 2)	
	N (%)		N (%)		N (%)	
Adverse Event	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Anemia	6 (37.5)	2 (12.5)	13 (44.8)	0 (0)	0 (0)	0 (0)
Neutropenia	3 (18.8)	6 (37.5)	3 (10.3)	2 (6.9)	0 (0)	0 (0)
Febrile Neutropenia	1 (6.25)		1 (3.45)		0 (0)	
Thrombocytopenia	7 (43.8)	1 (6.25)	10 (34.5)	1 (3.45)	0 (0)	0 (0)
Neuropathy	11 (68.8)	0 (0)	10 (34.5)	2 (6.90)	0 (0)	0 (0)
"Hand-Foot"	3 (18.8)	0 (0)	6 (20.7)	1 (3.45)	0 (0)	0 (0)
Mucositis	1 (6.25)	0 (0)	1 (3.45)	0 (0)	0 (0)	0 (0)
Diarrhoea	3 (18.8)	0 (0)	6 (20.7)	0 (0)	0 (0)	0 (0)
Nausea	9 (56.3)	0 (0)	13 (44.8)	2 (6.90)	1 (50)	1 (50)
Asthenia	2 (12.5)	0 (0)	9 (31)	0 (0)	1 (50)	0 (0)
Dose Reduction	2 (12.5)		9 (31)		0 (0)	
Treatment Suspension	4 (25)		3 (10.3)		1 (50)	
Cycles	Mean	Total	Mean	Total	Mean	Total
	5.44	87	5.69	165	4.50	9

Legend: EOX: Epirubicin, Oxaliplatin and Capecitabine; F+P: Fluoropyrimidine and Platinum; F: Fluoropyrimidine Monodrug

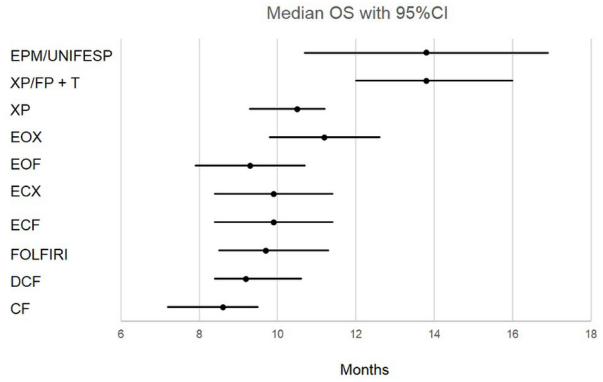

Figure 4. Median and 95% Confidence Interval for Overall Survival among Different Trials. 95%CI: 95% Confidence Interval; EPM/UNIFESP: Federal University of Sao Paulo; EOX: Epirubicin, oxaliplatin and capecitabine; ECF: Epirubicin, cisplatin and 5-fluouracil; FOLFIRI: Leucovorin, 5-fluouracil and irinotecan; DCF: Docetaxel, cisplatin and 5-fluouracil; CF: cisplatin and 5-fluouracil

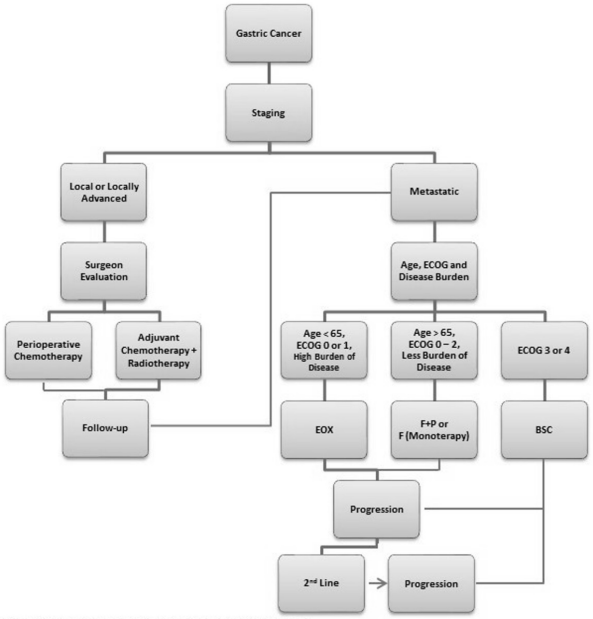

Figure 5. Institutional Guideline for the Treatment of Metastatic Gastric Cancer. HU/UNIFESP: University Hospital of Federal University of Sao Paulo; ECOG: Eastern Cooperative Oncology Group; EOX: Epirubicin, oxaliplatin and capecitabine; F/P: doublet of fluoropyrimidine and platin; F: fluoropyrimidine; BSC: Best Supportive Care

2). The factors for better prognosis of OS were identified to include second-line of treatment (HR: 0.25, 95%CI: 0.11-0.58) (Figure 3). However, some limitations of these results may arise because the study was not designed for this purpose; furthermore, the differences between the group receiving chemotherapy and the group receiving supportive care after first-line failure may be related to clinical rather than therapeutic issues. The other prognostic factor associated with better OS was response to treatment (HR: 0.23, 95%CI: 0.12-0.47). Diffuse histology was identified as a poor prognostic factor for OS (HR: 1.89, 95%CI: 1.22-2.88); this outcome was expected because of the established biology of gastric tumors.

Metastasis at more than 2 sites tended to be associated with an increased risk of death (HR 1.93, 95%CI: 0.92-4.08). The worst ECOG performance status (ECOG 2) also showed a trend in predicting the risk of death (HR 1.54, 95%CI: 0.81-2.94). These data were also expected, in accordance with the natural course of cancer.

Second-line Treatment

Of the 47 patients, 34 showed progression of disease and, of these, 14 (41.2%) were treated with second-line chemotherapy. The main second-line chemotherapy regimens were irinotecan + 5-FU (6 patients, 42.9%), taxanes (4 patients, 28.6%), oxaliplatin + 5-FU or capecitabine (2 patients, 14.3%), and 5-FU monotherapy (2 patients, 14.3%). There was an average of 3.1 cycles for the second-line treatments.

Regarding efficacy, 7 patients were evaluated for response to treatment, of these, only 1 (14.2%) showed partial response, 3 (42.9%) had stable disease, and 3 (42.9%) showed progression of the disease. The median PFS was only 3.6 months in the patients who received second-line therapy; however, patients who were treated with second-line regimens had higher OS than patients who discontinued first-line treatment (median 15.1 versus 7.9 months, respectively). These results encouraged the prescription for second-line chemotherapy whenever possible.

Adverse events (AEs)

The main AEs observed for patients treated with F+P and EOX were grade 1 and 2 nausea (13 [44.8%] and 9 [56.3%] patients, respectively), grade 1 and 2 neuropathy (10 [34.5 %] and 11 [68.8%] patients, respectively), grade 1 and 2 anemia (13 [44.8%] and 6 [37.5%] patients, respectively), grade 1 and 2 thrombocytopenia (10 [34.5%] and 7 [43.8%] patients, respectively), and grade 1 and 2 neutropenia (3 [10.3%] and 3 [18.8%] patients, respectively), and grade 3 and 4 neutropenia (2 [6.9%] and 6 [37.5%] patients, respectively).

Among patients treated with F+P and EOX, chemotherapy dose reduction was required in 9 (31.0%) and 2 (12.5%) patients, respectively, and treatment was discontinued in 3 (10.3%) and 4 (25.0%) patients, respectively. Table 3 shows the occurrence of AEs in accordance with the chemotherapy protocols.

AEs were managed medically, and there were no deaths secondary to systemic treatment.

Discussion

Patients in the study showed age and gender distribution characteristics that were comparable with most studies (Tong et al., 2014); however, a high proportion of patients showed a lower performance status. Two recent studies (Cunningham et al., 2008; Kang et al., 2009) reported that <15% of patients had an ECOG performance status of ≥2, whereas in this study, 31.9% had an ECOG performance status of ≥2. The number of metastatic sites shows a heterogeneous distribution in different studies; in the present study, almost one-third of the patients had ≥2 sites of metastases, and showed a trend for unfavorable OS.

This study was designed to evaluate the OS for patients with metastatic GC treated at a university hospital; a median OS of 13.8 months (95%CI: 10.7-16.9) was observed, which is comparable with that reported in the current literature. Figure 4 presents the median OS and 95%CI in this study, and the values obtained in the literature (Van Cutsem et al., 2006; Cunningham et al., 2008; Kang et al., 2009; Bang et al., 2010; Guimbaud et al., 2014). The most important limitation of this study was the small cohort of patients and its retrospective design. Because of this limitation, we should be careful while comparing results, especially with those from phase III studies with larger cohorts. Nevertheless, it is important to present these findings, as Brazilian data are scarce and there are many institutions with similar levels of service capacity in Brazil and other developing countries.

We propose that the median OS in the present study was high primarily because of the individualized treatment that was provided to patients. Unlike a phase III randomized trial, each patient in this study received treatment according to their baseline characteristics such as age, performance status, and disease burden. Therefore, it is important to develop an institutional protocol that favors individualized treatment, as is proposed in Figure 5 based on the results for our institution's population. This retrospective study was not designed to compare chemotherapy protocols and because of this, the results must be analyzed with caution. Furthermore, in this study, all differences between the outcomes for two-drugs or three-drugs regimens were not statistically significant; however, in terms of absolute numbers, EOX showed a better objective response rate than F+P, indicating that it may be an appropriate regimen for patients in the best clinical condition, with a high disease burden. Upon analyzing the median PFS and OS stratified by ECOG performance status, EOX was superior to F+P for patients with an ECOG performance status 0 or 1. For patients with an ECOG performance status 2, EOX achieved a lower PFS than F+P; EOX is also a toxic regimen, showing no cost-benefit relationship for this cohort. Our data are insufficient to recommend a three-drug regimen for patients aged ≥65 years, as only 1 patient met these treatment criteria. However, in a phase III study of 239 patients treated with EOX, the median age was 62 years (range: 25 to 80 years) (Cunningham et al., 2008). For patients aged <65 years, EOX achieved better PFS and OS than F+P; thus, it is a reasonable option in this cohort. A prospective trial is necessary to validate the protocol.

The choice of chemotherapy for first-line treatment of metastatic GC remains debatable. The classic treatment backbone for metastatic GC is a fluoropyrimidine plus a platinum agent regimen, and the addition of a third agent remains a subject of discussion. In a meta-analysis, Wagner et al. reported that the addition of anthracyclines improved OS (HR 0.77, 95%CI: 0.62 -0.95, 501 participants) (Wagner et al., 2010); however, significant treatment-related toxicity was observed (anemia and neutropenia of any grade were observed in 70% of the patients) (Cunningham et al., 2008; Wagner et al., 2010). Guimbaud et al. presented results that may enhance this discussion: in a phase III study of 416 patients, 5-FU + leucovorin + irinotecan (FOLFIRI) was compared with epirubicin + cisplatin + capecitabine (ECX). FOLFIRI was associated with a longer time-to-treatment failure (5.1 versus 4.2 months; p=0.01); no significant differences were observed in median PFS (5.3 versus 5.8 months; p=0.96), median OS (9.5 versus 9.7 months; p=0.95), or RR (39.2% versus 37.8%). AEs were less frequent with FOLFIRI than with ECX (overall rate of grade 3 to 4 toxicity: 69% versus 84%; p <0.001; hematologic AEs, 38% versus 64.5%; p <0.001) (Guimbaud et al., 2014). Upon analyzing all available data in the current literature we concluded that chemotherapy has a limit of no more than 12 months in terms of median OS; moreover, the addition of anthracycline as a third drug does not increase the treatment efficacy in the same proportion as it increases the toxicity. However, in our institution, treatment with a three-drug regimen is still the standard of care for younger and fitter patients with a high burden of disease.

In this study, the overall RR was 64.3% for patients treated with EOX, and 37.5% for those who received F+P. A phase III study reported 47.9% objective response for patients treated with EOX; this difference in outcomes may be explained by the difference in number of patients treated in each study (16 and 244, respectively) (Cunningham et al., 2008). Some phase II studies that evaluated the efficacy of treatment with two drugs reported an overall RR of 42% on average (range: 35% to 65%) that is consistent with the value obtained in this study (Jatoi et al., 2006; Park et al., 2006; Van Meerten et al., 2007). This study was not designed to compare various treatment protocols, so these findings must be analyzed carefully. The main limitation in the treatment efficacy evaluation of this study was the response analysis. The same radiologist could not conduct all exams, and we did not confirm the results with an internal or external radiologic service. The intervals between images were not identical for all cases. Moreover, different chemotherapy regimens were grouped and analyzed as F+P; however, despite the equivalence of 5-FU and capecitabine and of cisplatin and oxaliplatin presented in the REAL 2 trial (Cunningham et al., 2008), certain regimens such as Nordic-FLOX are not standard for the treatment of metastatic GC. Nevertheless, we believe that our findings are important for other centers facing similar limitations (temporary unavailability of capecitabine and definitive unavailability of 5-FU pump infusion) in Brazil and other developing countries.

After the ToGA trial, the addition of trastuzumab to chemotherapy became a standard of care for HER-2 positive metastatic GC, initially improving the median OS by >12 months, with tolerable toxicity (Bang et al., 2010). However, this therapy is not available in the Brazilian public health system.

The efficacy of second-line chemotherapy for metastatic GC remains debatable, as most available studies are small and have modest results. A recent phase III study included 133 patients, randomized to receive either best supportive care or second-line chemotherapy with docetaxel or irinotecan. The response rates were 16.7% and 10%, respectively. A benefit in OS was observed for the treated groups compared to the group receiving best supportive care (HR 0.66, 95%CI: 0.49-0.89; p=0.01).

No statistical significance was observed between the regimens prescribed as second-line treatments (p=0.12) (Kang et al., 2012). Although the higher median OS for patients receiving second-line treatment may be related to clinical rather than therapeutic factors, we recommend it whenever possible.

In conclusion, the treatment of metastatic GC at the clinical oncology division of the UNIFESP presented outcomes that were consistent with the reported literature. The chemotherapy regimens showed manageable AEs that did not limit the treatment of patients and were comparable with the AEs reported in other studies. Although we could not confirm the superiority of any particular protocol with the information currently available, we recommend that the patient's characteristics be considered in treatment choice. In addition, second-line chemotherapy should be considered whenever possible. A prospective study evaluating the outcomes of individualized treatment protocols is necessary to validate our recommendations.

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